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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *403-405 and 407-412* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *403-405 and 407-412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments of 11/28/2007 have been entered in full. Claims 1-402 and 406 are cancelled. The newly cancelled claims include claims which were rejected in previous office actions. All prior objection/rejections directed to cancelled claims are moot and hereby withdrawn.

2. Claims 403-405 and 407-412 are under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Rejection Claims 403-405 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained and hereby extended to new claims 407-412 as they depend from claim 403. Applicant's arguments filed 11/28/2007 have been fully considered but they are not persuasive. The rejection of record held that the recitation in independent claim 403, step (b) "forming a bud" creates a lack of clarity as to whether the recited step requires action on the part of the practitioner of the method to form a bud. Applicant argues (p.7) that, "it is clear from the specification that the only step required by the practitioner is that of injecting stem cells into a selected site in a patient's body." Thus, Applicant acknowledges that although step (b) (and, by implication, step (c)) has the form of a method step, the actual intent is to recite an intended outcome. The claim defines the invention. Claim 403, which has not been amended, still appears to recite a method step instructing the

practitioner to form a bud. This rejection could be overcome by an amendment to recite, "wherein the injected cells form a bud which grows to form an artery at said selected site, and wherein said artery integrates itself…"

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Rejection of Claim 404 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. Applicant's arguments filed 11/28/2007 have been fully considered but they are not persuasive. The rejection of record holds that claim 404, which first appeared in the record in the amendment of 11/03/2006, introduces new matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection finds no support for the limitation of administration of cells to a damaged site in a leg of a patient in the specification as originally filed.
7. Applicant argues (p.9) that, "The Examiner has failed to explain where in claim 404 in calling for "injecting stem cells...at a damaged site" in a patient's leg defines subject matter completely outside the scope of the specification." First, it would be hard for any limitation to be completely outside the scope of the specification or to lack as least some mention in the specification. The instant specification puts forth a genus of "growth factors" that includes,

apparently, all of the molecules that are generally recognized as growth factors, plus all of the genes encoding such molecules (although genes are not mentioned in the definition on pages 20-21 of the specification), plus all living organisms, including all kinds of cells, and unspecified organic and inorganic matter. As previously noted, the specification broadly asserts that the administration of any of these myriad factors can achieve diverse effects. Applicant then expects that that any time any single member of this genus is mentioned in the specification one skill in the art would, without prompting, not only think of all other members of the genus, but also think of the particular species Applicant has in mind.

8. Secondly, there is no need to show that the subject matter is completely outside the scope of the specification. The rejection of record pointed out that, in *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971), the court ruled that a subgenus range was not supported by generic disclosure and specific example within the subgenus range. Here "in the body" is a generic disclosure, supported by the specification and recited in claim 403. Claim 404 recites, "a damaged site in a leg", which is a subgenus range, and the artery of Example 18 is a specific example within the subgenus range. Therefore, the specific teaching of an artery in Example 18 (setting aside for the moment the fact that Example 18 does not teach the administration of cells) does not support the subgenus (a damaged site in a leg) recited in claim 404, even though both the species and the subgenus are within the scope of "in the body".
9. Applicant submits (p.9) that all the limitations of claim 404 appear in the specification as originally filed. Applicant further asserts (p.9) "The specification is replete with description of inserting a soft tissue growth promoter at a desired (damaged) site in the body (pages 10, 18, 20, 21, 31, 32, 45, 52, 53, 56, and 62)", and further that, "Appropriate compositions which

promote the growth of soft tissue within the scope of Applicant's invention are described as comprising a patient's own cells (pages 47 and 48) and particularly stem cells (pages 37, 40, 41, 42, 48, 51 etc.) including autologous and allogeneic global bone marrow stem cells (bone marrow mononuclear cells/BMCs) and adult stem cells collected from peripheral blood." It is noted that when many of these same pages were addressed in paragraph 32 of the previous office action, Applicant complained that the "paragraph is gratuitously concerned with non-elected inventions and thus lacks focus upon the claimed invention" (Remarks, page 18).

10. The following table summarizes the teachings that Applicant has cited.

Table 1.

Page	Site	Material to be inserted	Asserted Outcome
10	Dental implant	Inert materials (bone, hydroxyapatite, etc) ; "allografts"	tooth
18	Dental implant	" active compositions, or tissue growth factors, can be intermixed with hydroxyapatite or other materials "	tooth
20	Dental implant; The body	Growth factors. This page includes the broad definition of growth factors.	"hard tissue" or bone and "soft tissues" like ectodermal and mesodermal tissues
21	The body	Growth factors; continuation of page 20.	
31	Jaw bone; The body	Tooth bud; genes which cause the morphogenesis and further growth of other organs or hard or soft tissue; "genetically produced materials"	grow, reproduce, and replace leg bone, facial bone, and any other desired soft and hard tissue in the body.
32	organ or other hard or soft tissue at a desired location or location(s) in the body	Genes; genetic material	create and grow morphogenetically in vivo organs or other hard or soft tissue; tooth

37	an artery wall	a soft tissue implant	an additional heart could be grown from a genetic implant
37	None specified	"Multifactorial and nonspecific cells (such as stem cells and germinal cells)"… "any host cell, cloned cell, cultured cell, or cell would work"	None specified
40	Not specified. Presumably jaw	Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques.	Growth of a tooth
41-42	body near a large artery	Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques.	A primitive kidney germ is produced…. As the kidney grows, its blood supply will be derived from the artery.
45	into muscle at a desired site.	gene or other genetic material; VEGF genes	An artery can be grown in the heart, legs, or other areas
45	Pre-existing organ	a gene to form cardiac muscle and/or an injection of a gene to form an artery	revive or replace the dead portion of the heart; Portions of organs throughout the body can similarly be repaired or replaced.
47-48	on or in the patient.	a skin cell(s) is removed from the intraoral lining of a cheek; one of the patient's own cells…a cell not originally obtained from the patient is inserted ;	Organs and/or tissues can be formed; growth of an artery, of pancreatic Islet cells, of a heart, etc
		germinal cells (and in some cases, stem cells)	differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro
51	none	Stem cells associated with the central nervous system	differentiate to neurons, astrocytes, and oligodendrocytes.
52	into or onto the body at a specific location	a gene, growth factor, ECM (or other genetic material) and/or	induce and promote the morphogenesis and growth of an organ or desired organ sub-

		nutrient media	structure at that location
52	cell or group of cells outside the body	gene or other genetic material	The resulting induced organ or other structure is transplanted to a desired location in a patient's body
52	a selected location or locations in the body	a gene and a growth factor; a growth factor and the extracellular matrix	grow a selected organ or structure; grow an organ
53	damaged one inch long section of a large artery in his left leg; first site is on the exterior wall of the artery; The second site is inside the wall of the artery on the other side of the lower end of the artery	Recombinant cDNA encoded to combine with a cell ribosome to produce the human growth factor VEGF	new growth at the first and second sites; new artery growing adjacent the patient's original artery has grown to a length of about one inch and has integrated itself at each of its ends with the original artery such that blood flows through the new section of artery
56	cardiac muscle immediately adjacent a clogged artery	cDNA clones for recombinant human VEGF165,	collateral artery formation; One end of the artery integrates itself in the heart wall to receive blood from the heart. The other end of the artery branches into increasing smaller blood vessels to distribute blood into the heart muscle.
62	two sites in the coronary artery	Recombinant cDNA encoded to combine with a cell ribosome to produce the human growth factor VEGF	a new section of artery grows integral with the original artery, and two sites in the coronary artery

11. The claim in question specifically recites a subgenus of cells, stem cells, for the purpose of growing a specific type of organ, an artery, at a specific site, a damaged site in a leg of a patient. A seen in table 1, pages 10, 18, 20, 21, 31, 32, 37, 40, 41, and 52 generically teach organs or tissues, but not the recited artery. Examples 15 and 16 (pages 41-42) suggest that stem cells from bone marrow or blood may be used to grow kidneys, not the claimed species of organ. Example 17 has a section directed to formation of an eye, but also includes a

teaching (p.45) directed to artery formation which suggests "injecting a gene or other genetic material" (lines 2-3), VEGF genes (lines 10-11) or VEGF proteins (lines 13-15); no cells are mentioned. Pages 47-48 mentions stem cells, among other cell types, and an artery, among other organs, but does not recite a damaged site in a leg. Example 18 (p.53) mentions legs, but teaches the use of recombinant DNA and does not reasonably suggest the use of any kind of cell to grow an artery. Examples 19 (p.55-56) and 35 (page 62) mention coronary arteries, not an artery in a damaged site in a leg, and like Example 18, Examples 19 and 35 teach the use of recombinant DNA and do not reasonably suggest the use of any kind of cell to grow an artery. The combination recited in claim 404, requires the selection of "artery" from the genus of organs and soft tissues; selection of "stem cells" from the large genus of growth factors encompassed by Applicant's broad definition, and selection of a damaged site in a leg' from the genus of "the body". The specification does not suggest or contemplate the claimed combination. These teachings do not *reasonably* lead to the specific use of stem cells or the specific location in the leg, as required by claim 404. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

12. Applicant argues (pp.10-12) that the Examiner's reliance on case law relating to genus-species requirements misses the point and that the present Examiner is bound by his and prior PTO holdings. By "prior holdings", Applicant refers to the recognition that *the lexicon of this specification*, provides for a broad definition of "growth factor" that may be construed to

include "cells", and to the election of species that was required earlier in the prosecution of this application. To review, the requirement for restriction/election mailed on 02/24/2004 set forth 24 patentably distinct species (a-x) of "growth factor" based on the various functional and structural definitions found in the specification. The list indicated that several individual species of growth factor (*e.g.* species d-n) as well as several species that are actually drawn to large classes of products {a), b), c), p), r), s), t), u), v), w) and x)}, are patentably distinct. Applicant was required to elect a single product or structure if any of the latter species were elected. Applicant elected (03/03/2004) species a) "living organism", which was subsequently determined to include "cells". Applicant now argues that by pointing out that "cells" and "VEGF cDNA" are so structurally and functionally distinct that they must belong to distinct subgenera within "growth factors", the argument set forth in the office action of 07/24/2007 somehow violates previous holdings. Is Applicant contending that VEGF cDNA is a living organism? Applicant cannot transmute one substance into another simply by changing the definition. The fact that individual growth factors (or their encoding nucleic acids) are not cells or a living organisms has been consistently recognized throughout the prosecution of this case, as evidenced by the species election without traverse on 03/03/2004. The rejection of record holds that, by evoking Example 18, Applicant relies on one specific example within the genus of growth factors (VEGF cDNA) to support a subgenus (stem cells) that is clearly distinct in its structure and mode of action. There simply is no rational scientific basis for one of skill in the art to read "VEGF cDNA" and think "stem cell", without being specifically prompted to do so. The instant specification does not provide that prompting. Applicant has asserted (p.12) that Dr. Elia was the first to recognize that VEGF,

cDNA, and stem cells are equivalent species within the genus soft tissue growth promoters for growing arteries in a human patient. In so arguing, Applicant implicitly acknowledges that at the time the instant application was filed, methods of *in vivo* treatments involving administration of whole live cells as opposed to nucleic acids had a different status in the art such that it is well known that cell therapy and gene therapy are not obvious variants of one another. Therefore, for one of skill in the art to *even think* of extrapolating example 18 to guide the use of cells, the skilled artisan would have to already know the very thing that Applicant claims to have been the first to discover. The instant specification does not provide any evidence to cause the skilled artisan to make this conceptual leap.

13. Applicant next argues (p.12-13) that with the issuance of U.S. Patent No. 5,980,887 (hereinafter "Isner '887) and U.S. Patent No. 5,328,470 to Nabel et al. (of record) the PTO has treated cells and genes as a class. Applicant asserts that the scope of claims issued by the PTO for Isner '887 encompass "VEGF cDNA" and "cells" as species of angiogenetic promoters, not different inventive entities. Firstly, this line of argumentation cannot be persuasive because, each patent application is evaluated on its own merits. Therefore, no response to this argument would be necessary. Nevertheless, the following response is provided to show that the cited patents support rather than undermine the Examiner's position.

14. On what basis does Applicant assert that cells and genes are treated as a class in Patent No. 5,890,887? Applicant apparently refers to the following claims:

> Claim 1. A method for inducing for inducing the formation of new blood vessels in an ischemic tissue in a patient in need thereof, comprising: administering to said patient host an effective amount of an isolated endothelial progenitor cell to induce new blood vessel formation in said ischemic tissue,…

2. The method of claim 1, further comprising the step of administering to the patient an endothelial cell mitogen or a nucleic acid encoding an endothelial cell mitogen.

3. The method of claim 2, wherein the endothelial cell mitogen is selected from the group consisting of acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor, insulin like growth factor, erythropoietin, colony stimulating factor, macrophage-CSF, granulocyte/macrophage CSF and nitric oxide synthase.

15. Clearly it is possible to claim and perform a method in which cells, cDNA, and/or polypeptide growth factors are used together, as Isner '887 has done in dependent claims 2 and 3, for example. Applicant, however, is not arguing that cells and various molecules can be used to complement one another to achieve an end. Rather, Applicant relies on the notion that a teaching of cDNA for growing an artery intrinsically and inherently causes one of skill in the art to envision using stem cells for the same purpose. The allowed claims in the '887 patent do not indicate that each of the recited components are interchangeable. If a teaching of "cells" inherently encompasses cDNA and protein factors, then why bother with dependent claims that recite these *further* components? If recitation of cDNA encompasses cells, why is claim 1 separate from the others? The Isner '887 patent does not support the assertion that the USPTO has ruled that one of skill in the art would read a teaching about genes or protein growth factors and thereby envision the use of stem cells for the same purpose.

16. Applicant's citation of U.S. Patent No. 5,328,470 to Nabel et al. is inexplicable. The allowed claims are drawn to kits comprising DNA and various optional additional factors and/or a means for causing a cell attached onto the walls of a vessel or in an organ or tissue in said patient to express an exogenous therapeutic agent protein. That is, the claims are drawn to

various molecules can be used to complement one another to achieve an end. This does not indicate that cells and genes are treated as a class.

17. Applicant next (p.12) cites U.S. Patent No. 7,097,832, to Kornowski et al. as evidence that the use of endothelial progenitor cells as taught in Isner '887 does not achieve artery growth. This does not speak to the immediate question of whether the instant specification as filed conveys to one of skill in the art that Applicant was in possession of the claimed method. This reference, and its associated argument, will be addressed with respect to enablement.

18. Applicant has correctly pointed out that to comply with the written description requirement of 35 U.S.C. 112, first paragraph, 'the applicant must.., convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. One cannot ignore *reasonable clarity*. The instant specification as filed, taken as a whole and in view of Applicant's cited pages therein, does not reasonably lead the skilled artisan to the recited combination of the agent to be administered, the desired result, and the site of administration. Therefore the introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 constitutes new matter.

19. Rejection of Claims 403-405 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained and hereby extended to include new claims 407-412. Applicant's arguments filed 11/28/2007 have been fully considered but they are not persuasive. It is first noted that Applicant characterized the introductory statement in the rejection of record, analogous to the first two sentences of this paragraph, as a perfunctory

conclusion that does not address the previous grounds with specificity (remarks, p. 13). Applicant apparently failed to notice that the introduction was followed by 10 pages of text addressed to Applicant's arguments with respect to the reasons of record. Applicant levels a similar charge again on page 25, where Applicant alleges that "the present Examiner has not repeated or specifically addressed the enablement rejection of the prior Examiner based upon the factors described In re Wands. Certainly, the Examiner did not specifically comment as to why the prior remarks of Applicant regarding these factors were not persuasive." In response, it is noted that the previous office action addressed *the breadth of the claims* and the *amount of direction or guidance present and the presence or absence of working examples.* The present office action is similarly directed. It is herein noted that the breadth of the claims as currently amended is considerably narrowed in reciting a single organ, an artery, and a subgenus of cells, stem cells. The latter subgenus is still large, however, as the term "stem cell" includes embryonic stem cells, neural stem cells, amniotic epithelial cells, and mesenchymal stem cells, to mention those cited in references of record. As noted previously, and reiterated herein, the instant specification did not disclose with specificity which cells would or would not work for growing an artery. Thus, the breadth of the term "stem cell" cannot not be supported by an enabling disclosure. The remaining arguments presented herein are clearly directed to amount of direction or guidance present and the presence or absence of working examples. Applicant is hereby advised that the following is addressed to Applicant's arguments filed 11/28/2007.

20. Applicant first makes reference to Applicant's co-pending Application Serial No. 10/179,589. In that application, claims have been rejected on the grounds of double patenting as claiming

a nearly identical scope to the instant claims. Like the instant claims, the corresponding claims in the '589 application have been rejected under 35 U.S.C. 112, first paragraph, but in the rejection in the '589 application have been deemed to be enabling for a scope that includes a method of growing and integrating a desired artery at a selected site in a body of a human patient comprising the steps of locally placing a CD34+ mononuclear cell harvested from bone marrow or peripheral blood in a body of a human patient. Applicant suggests that a similar determination of enablement would be in order for the scope of subject matter set forth in the present claims, in view of the aforementioned double patenting rejection and the commonality of the disclosures. This is not persuasive for the following reasons.

21. Neither the instant disclosure nor '589 application teaches one of skill in the art how to perform the claimed method of growing an artery using stem cells. However, *the state of the art* is a factor that must be taken into consideration in determining enablement. Claims filed in 2002 reciting methods to grow an artery using stem cells cannot be said to totally lack enablement because, by then, the state of the art had changed so that such a method was known to be possible. This change in the state of the art is evidenced by US Patents 5980887 and 7097832, which were cited as anticipatory disclosures under 35 U.S.C. 102(e) in the office action mailed on 08/31/2007 in the '589 application. Thus, the rejection in the '589 application stated that the scope of enablement is supplied solely by that which is known in the art, based upon disclosures that occurred after the filing of application 09/064,000, in order to make it clear that, *by themselves*, neither the instant disclosure nor the '589 disclosure would support any scope of enablement. Thus the instant claims can be rejected as lacking enablement, whereas similar claims in the '589 application are afforded a scope of

enablement supported by the state of the art. Neither of Applicant's disclosures could possibly have guided or contributed to others' success in developing the method.

22. Next, Applicant (p. 14) suggests that the specification (pages 20, 21, 30-32, and 38-42) provides a substantial body of disclosure regarding using a growth factor to form a bud and grow soft tissue in a human body and that pages 10, 20, 21, 31, 32, and 37-52 describe "a class of growth factors that broadly and specifically includes genes, nucleic acids, a patient's own cells (autologous cells), or universal cells, e.g., stem cells (global mononuclear bone marrow cells), etc., all of which are described to promote tissue growth through differentiation and morphogenesis." Applicant complains that the Examiner has only considered the disclosure regarding enablement as it specifically relates to the elected growth factor species, cells, "which ignores Applicant's broad and specific disclosure relating to non-elected growth factor species disclosure". This is not persuasive for several reasons. First and foremost is the fact that the instant claims are specifically drawn to using stem cells to grow an artery. It is altogether proper for the examination to focus on the teachings of the specification that are directed to the claimed methods. Secondly, Applicant's argument on page 14 contradicts the argument on page 18, wherein Applicant complained that when teachings on pages 20, 32, 46, 47, 47, and 50 of the specification were addressed in paragraph 32 of the previous office action, the "paragraph is gratuitously concerned with non-elected inventions and thus lacks focus upon the claimed invention".

23. While the lexicon of this specification permits the examination of claims reciting administration of cells after Applicant had elected the species "living organisms", it is a separate question whether broad disclosures such as those on pages 10, 20, 21, 30-32, and

37-52 can teach one of skill in the art how to make and use the claimed invention. The teachings of specification pages 20, 32, 45, 46, 47, 47, 50, and 52 have been addressed on the record with respect to the instant claims (see office action mailed 07/24/2007 at paragraphs 32-33). The rejection of record examined the sections of the specification that Applicant had selected as purporting to support the limitations of the instant claims and found that not one of them teaches one of skill in the art how to use any kind of cell to grow an artery. Of the additional pages cited above, it is first noted that page 10 does not mention any kind of cell; the closest teaching is the generic term "allograft", which is present in a context that is suggestive of "bone allografts" (page 10, lines 1-13). Page 21 continues the broad definition of "growth factors" that began on page 20. No cells are mentioned on page 21, which underscores the fact that the specification never clearly enunciates the concept that Applicant intended that "bone marrow stem cells" were meant to be included as a species of "growth factor", even under Applicant's broad definition (see office action mailed 07/24/2007 at paragraph 29). Likewise, pages 30-32 do not mention cells. Page 37 (lines 10-13) asserts that "Sticky cells can be used to attach genetic implants to selected sites", which is followed by the fantastic speculation, "In this manner, an additional heart could be grown from a genetic implant." Page 37 also teaches, "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated." The nonsensical nature of this teaching has been documented in the record (action mailed 07/24/2007 at paragraphs 19-22). Whatever this means, it certainly does not suggest the use of cells to grow an artery, nor does it provide any guidance as to how to use stem cells to grow an artery. In

fact, the sentence states, "Likewise, any host cell, cloned cell, cultured cell, or cell would work", far from guiding the skilled artisan on how to perform a specific method, would have the skilled artisan believe that any cell can do anything. Applicant draws attention to pages 38-42. This section comprises Examples 1-14, which are apparently directed to formation of a tooth, Example 15, which is directed to formation of a kidney, and Examples 16-17, which are directed to formation of an eye. In examples 13 and 14, the artisan is instructed to apply an electric spark to stem cells in order to activate MSX-1 and MSX-2 genes. In Examples 1-4, 10, and 11-17 the artisan is instructed to remove genes from skin tissue of a patient and then the artisan is given the nonsensical instruction to store the genes in nutrient culture medium. The genes are then to be added to culture medium along with stem cells, which apparently will result in growth of a tooth, kidney, or eye, depending on the genes used. This section does not set forth a credible procedure to produce the asserted results and does not even mention growth of an artery.

24. A central theme of Applicant's remaining arguments was actually introduced on page 12, "What the Examiner has failed to appreciate is that on this record Dr. Elia was the first to recognize that VEGF, cDNA, and stem cells are equivalent species within the genus soft tissue growth promoters for growing arteries in a human patient. This is a material fact established on this record regardless of Applicant's manner of "reduction of practice" for the present invention." In so arguing, Applicant implicitly acknowledges that at the time the instant application was filed, methods of *in vivo* treatments involving administration of whole live cells as opposed to nucleic acids had a different status in the art such that it is well known that cell therapy and gene therapy are not obvious variants of one another. The rejection of record points out that

Applicant seeks to change the state of the art, but does not teach the skilled artisan how to apply Applicant's alleged novel understanding to a working method. The instant specification does not show a single organ, part of an organ, tissue, artery, or even a bud formed by placing cells in a body. Applicant claims to have achieved something no one else had done, and then claims to have achieved it simply by writing it down. To say that the novel, non-obvious, and remarkable result of growing an artery by administering stem cells can be achieved without doing a single experiment is incredible. Thus, when Applicant now argues (pages 15-17) that the instant application teaches one skilled in the art how to make and use the invention simply because "the materials and administration techniques, but not the inventive results, were well known when the instant application was filed", the argument is not persuasive because the instant specification discloses only speculation and *does not disclose any inventive results*.

25. In response, Applicant complains (page 18), "The Examiner's remarks seem to require a standard not found in the patent statute—a requirement for an actual reduction to practice to support patentability." Applicant argues on page 19, "…compliance with the first paragraph enablement requirement of Section 112 does not depend on the presence of an example, whether actual (working) or prophetic." Again on page 22, "The Examiner in paragraphs 44, 45 and 46 authors a general patent-defeating theme that a prerequisite for obtaining a patent is that there must have been an actual reduction to practice. On page 23, "Examiner fails to appreciate that the act of "writing down" a "prophetic" example which describes an embodiment based upon predicted results rather than work actually conducted is sufficient to satisfy a constructive reduction to practice."

26. First, it is important to distinguish the separate issues that arise under 35 U.S.C. 112, first paragraph. Except for claim 404, the instant claims are not presently rejected as failing to meet the written description requirement. Even if the specification is deemed to teach a concept, thereby meeting the written description requirement, it is a separate question whether the specification teaches one of skill in the art how to make and use the claimed invention. Applicant's argument ignores the fact that proof of a constructive reduction to practice requires sufficient disclosure under the "how to use" and "how to make" requirements of 35 U.S.C. 112, first paragraph. Kawai v. Metlesics, 480 F.2d 880, 886, 178 USPQ 158, 163 (CCPA 1973). As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but **more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity**. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Conception and reduction to practice occur simultaneously in certain circumstances. Alpert v. Slatin, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962). "[I]n some **unpredictable areas of chemistry and biology**, there is no conception until the invention has been reduced to practice." MacMillan v. Moffett, 432 F.2d 1237, 1234-40, 167 USPQ 550, 552-553 (CCPA 1970). See also Hitzeman v. Rutter, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001) (conception simultaneous with reduction to practice where appellant lacked reasonable certainty that yeast's performance of certain intracellular processes would result in the claimed antigen particles); Dunn v. Ragin, 50 USPQ 472, 475 (Bd. Pat. Inter. 1941) (a new variety of asexually reproduced plant is conceived and reduced to practice when it is

grown and recognized as a new variety). Under these circumstances, conception is not complete if subsequent experimentation reveals factual uncertainty which "so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994).

27. Even if interpreted in Applicant's most favored light, the most precise description of the cells to be administered in the instantly claimed methods is "bone marrow stem cells". Applicant did not distinguish between what is now being referred to as "global bone marrow stem cells" (a term used in Applicant's response, but not in the instant specification) and CD34+ mononuclear cells disclosed in Isner '887 (of record), for example. It was in fact Isner '887 who made the discovery that the CD34+ mononuclear cell population, present in both bone marrow and peripheral blood, comprises progenitors for endothelial cells as well as the previously identified hematopoietic progenitors. Applicant cites (p.12) U.S. Patent No. 7,097,832, to Kornowski et al. (of record as Exhibit B; submitted 11/28/2007) as evidence that the use of endothelial progenitor cells as taught in Isner '887 does not achieve artery growth. Applicant does not say where in the '832 specification this is taught, and the Examiner could not find any evidence that the '832 patent discloses any comparison that would support this conclusion. Isner's work is not mentioned in the text of the '832 specification, although several Isner publications were apparently considered during prosecution. The '832 patent and Isner '887 seem to be in general agreement as they each disclose cells derived from bone marrow as being able to stimulate neovascularization. The relationships among these cells remains uncertain, as is the precise population of cells that give rise to endothelial cells, as evidenced by Rabelink *et al.*, Arthrosclerosis and Vascular Biology, 24:834-838, (2004) (referred to by Applicant as "article

published by the American Heart Association entitled, "Endothelial Progenitor Cells: More Than an Inflammatory Response" and entered into the record as Exhibit C, 11/28/2007), at p. 835. Therefore, the '887 and '832 patent disclosures and the Rabelink *et al.*, reference represent subsequent experimentation that reveals factual uncertainty which "so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." See Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994), cited above.

28. Even without post-filing references indicating uncertainty, Applicant's specification did not disclose with specificity which cells would or would not work for growing an artery. In some places it could be any cell. In others it is a skin cell that has undergone a mysterious process of dedifferentiation and redifferentiation. It might be a "germinal cell" "or in some cases stem cells". The cells are described as being "multifactorial and nonspecific", which does not provide any meaningful limitation as to the cells to use (see paragraphs 6-25 of the office action mailed 07/24/2007). Applicant has argued that one of skill would infer "stem cells" from sections of the specification that do not even mention any kind of cell. It has been shown repeatedly in this office action and in prior office actions that the very idea that bone marrow stem cells are to be used to grow an artery requires the skilled artisan to select this species out the infinitely large genus of factors applicant has defined. The concept of using any kind of cell to grow an artery relies on selection of portions of the specification that contain the desired words, interpreting them in a manner that is contrary to the ordinary meanings of the key terms in the art, and putting them together, without specific prompting in the specification. Applicant has argued that one of skill would infer "stem cells" from sections of the specification that do not even mention any kind of cell. This is not merely a matter of written

description, where the question is whether one of skill in the art can conceive the invention, this is also a matter of set forth the invention in such full, clear, concise, and exact terms to enable a person of skill in the art to make and use the claimed methods. Thus, to say that "Applicant claims to have achieved something no one else had done, and then claims to have achieved it simply by writing it down" does not fully describe the how the instant specification fails to provide an enabling disclosure for the claimed methods. The record is replete with examples of how the even the writing that Applicant relies upon does not set forth the invention in such full, clear, concise, and exact terms to enable a person of skill in the art to make and use the claimed methods.

29. Applicant draws attention to another such example on p. 18 of the Remarks, where Applicant makes reference to the specification at pages 47 and 48 and alleges the following:

> the art skilled is told that "reimplanting" a "patient's own stem cells results in differentiation and morphogenesis of a organ, i.e., artery, in a human patient."

Here, Applicant engages in obfuscation. The phrase, "patient's own stem cells results in differentiation and morphogenesis of a [sic] organ, i.e., artery, in a human patient" is presented as a quote from the specification, but no such phrase is to be found in the specification. Applicant has joined parts of sentences from separate paragraphs in an attempt to make it appear that the teaching in the specification is more explicit than it actually is. The sources appear to be, "In the example above, if germinal cells (and in some cases, stem cells) are utilized a ([sic] to?) direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro", from page 48, lines 13-15, and "A cell nutrient culture may or may

not be utilized depending on the desired functional outcome (i.e., growth of an artery, of pancreatic Islet cells, of a heart, etc.) or other circumstances", from page 48 lines 2-4.

30. It is understandable why Applicant would wish to edit this muddled section of the specification. "The example above" refers to the following paragraph, beginning on page 47:

> Organs and/or tissues can be formed utilizing the patient's own cells. For example, a skin cell(s) is removed from the intraoral lining of a cheek. The cell is genetically screened to identify DNA damage or other structural and/or functional problems. Any existing prior art genetic screening technique can be utilized. Such methods can utilize lasers, DNA probes, PCR, or any other suitable device. If the cell is damaged, a healthy undamaged cell is, if possible, identified and selected. If a healthy cell can not be obtained, the damaged cell can be repaired by excision, alkylation, transition or any other desired method. A growth factor(s) is added to the cell to facilitate dedifferentiation and then redifferentiation and morphogenesis into an organ or function specific tissue. Any machine known in the art can be used to check the genetic fitness of the organ and its stage of morphogenesis. A cell nutrient culture may or may not be utilized depending on the desired functional outcome (i.e., growth of an artery, of pancreatic Islet cells, of a heart, etc.) or other circumstances. Replantation can occur at any appropriate stage of morphogenesis. The foregoing can be repeated without the patient's own cells if universal donor cells such a germinal cells are utilized. Germinal cells do not require a dedifferentiation. They simply differentiate into desired tissues or organs when properly stimulated. Similarly, the DNA utilized in the foregoing procedure can come from the patient or from any desired source.

31. Thus, "the example above" exemplifies a skin cell(s) is removed from the intraoral lining of a cheek. The artisan is instructed to screen for DNA damage, apparently any kind of damage to any gene, as no specific criteria are set forth to distinguish between "healthy" and "unhealthy". Likewise, the subsequent instruction to check genetic fitness is unclear—since this is supposed to be a new method, what constitutes "genetic fitness"? what genes are involved? and what machine does one use to determine it? The method then cites processes of DNA repair that can occur in intact cells, but does not teach how cells are to be induced to effect the desired repair. The method then suggests the addition of some unknown and

undefined growth factors after which the cells can undergo processes of dedifferentiation and redifferentiation followed by morphogenesis into any desired organ or tissue. No such growth factor regimen is known in the art, and the specification does not teach one. It is not clear what "germinal cells" are but they are suggested to differentiate into desired tissues if properly stimulated. How to properly stimulate them to form an artery or any other organ is not disclosed. Consider also the instruction that, "A cell nutrient culture may or may not be utilized depending on the desired functional outcome." The specification (p.41) contains the following definition: "The term "cell nutrient culture" as used herein can include any or any combination of the following: the extracellular matrix; conventional cell culture nutrients; and/or, a cell nutrient such as a vitamin. As such, the cell nutrient culture can be two-dimensional, three dimensional, or simply a nutrient, and is useful in promoting the processes of cellular dedifferentiation, redifferentiation, differentiation, growth, and development." By this definition, the phrase, "A cell nutrient culture may or may not be utilized" refers to the use of multiple agents that act upon cells. But the specification does not teach any factors or combination of factors that cause any cell to form an artery. "The example above", therefore, suggests that novel combinations of growth factors, ECM, nutrients, and vitamins will be able to cause cells to dedifferentiate, redifferentiate and form any organ or tissue, but does not teach what these combinations are.

32. So, even if "In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ" (specification p.48) is taken to mean that stem cells are to take the place of the skin cells or germinal cells of the example, so that use of stem cells to grow an artery is "contemplated", as Applicant argues

on page 18, it does not even begin to teach one of skill in the art how to use stem cells to grow an artery. The cited section of the specification generally points toward some of the complex problems that might be encountered in regenerative medicine (choosing the right cell type, the possibility of preexisting genetic damage in the cells, the multiple factors that may direct pluripotent cells to differentiate in specified pathways) but does not teach the skilled artisan any solution to these problems. The specification tosses out the idea that something can be done and then invites the skilled artisan to figure out how to do it.

33. Lest Applicant should argue that the discussion of such topics as DNA repair, genetic fitness, dedifferentiation, redifferentiation, cell nutrient culture, and the vagueness of the term "germinal cells" are "gratuitously concerned with non-elected inventions and thus lacks focus upon the claimed invention", Applicant is reminded that Applicant has repeatedly asserted that the entire disclosure should be read and considered.

34. Applicant addresses (pp.19-20) the question of extrapolation of dosages of a VEGF cDNA construct, taught in Example 18, to calculate a number of stem cells to use in a method wherein stem cells are used in place of the cDNA construct. It is important to remember why the subject of converting an amount of plasmid DNA to cellular equivalents entered into this discussion in the first place. Firstly, lack of guidance in the instant specification was addressed as part of the *Wands* analysis in the rejection of record (office action mailed 02/07/2007, pages 9-13). The Strauer, Circulation (2002) reference of record was cited as an example of the detail and experimentation that would be required for an enabling disclosure. The rejection did not specifically mention the absence of guidance as to how many stem cells should be used to grow an artery. However, Applicant apparently feels that, if guidance for this single detailed aspect of the claimed method were to be demonstrated to be present in the specification, the rejection of

record would be overcome. It would not. Nevertheless, Applicant argues that Example 18, not only suggests the use of stem cells to grow an artery, it provides guidance in the number of cells to use, because one of skill would extrapolate an appropriate cell number from the quantities of plasmid DNA taught in the specification. No such extrapolation is taught the instant specification. A specific method for making this extrapolation was first entered the record in this case only as Exhibits D of the Lorincz and Heuser declarations filed on 05/25/2007. Therefore, this extrapolation is only under discussion because Applicant apparently seeks to establish that an extrapolation of this type is so well known in the art that it would be implicitly understood to be present in example 18 of the specification. The rejection of record holds that one of skill in the art would never think to attempt such an extrapolation because its scientific basis is unsound. Applicant's current response is merely a reiteration of arguments that have been addressed in the record.

35. Applicant now argues that "such extrapolations have been used for decades in the medical arts in regard to cell therapy. That which is well known in the art need not be included in Applicant's specification in order to comply with the enablement." This has been addressed in the record. Drs. Lorincz and Heuser concluded that the conversion depicted in Exhibit D is *consistent* with the extrapolations that have been performed for over 50 years. This carefully worded conclusion is not challenged. It, remains undisputed, however, that the consistency extends only to the point that the extrapolations involve math and DNA; any further comparisons would be impossible. The historical facts remain. See the office action mailed 07/24/2007 at paragraph 38, which established that scientists 50 years prior to the filing date of the instant application (1998) would not recognize the terminology or even imagine the

concept of the conversion depicted in Exhibit D. It is, therefore, impossible for Applicant's statement that "such extrapolations have been used for decades in the medical arts in regard to cell therapy" to be true. If, as Applicant contends, the use of the amount of recombinant plasmid DNA in a gene therapy protocol to calculate the number of stem cells to use in a cell therapy procedure is well known in the art, then numerous examples of extrapolations like the one in question should easily be found in the peer-reviewed scientific literature or the patent literature. Such an example would refute the Examiner's position more certainly than any carefully worded declaration that cites a "consistency" between calculations. Applicant has not provided any such example.

36. Applicant believes that the dosage extrapolation and the opinions in regard thereto expressed in the Declarations of Drs. Heuser and Lorincz "speak for themselves" (Response, p.20). As noted in the office action mailed 07/24/2007, at paragraph 40, the fact that the Declarants did not refute or address the proportional inequality of gene dosage between plasmid and genomic DNA also speaks for itself. The calculation in paragraph 39 the office action mailed 07/24/2007 made the point that the mole ratios of VEGF gene to total DNA are so radically different that it is fundamentally illogical to equate phVEGF$_{165}$ plasmid DNA with cellular genomic DNA on a per weight basis. Applicant has declined to present an argument to refute this.

37. Furthermore, the difference in gene dosage is just one reason why a person of skill in the art would never attempt such an extrapolation. The rejection also pointed out that delivery of genes to a target as recombinant DNA is a technically different process as compared to delivery of native genes within a living cell. No person of skill in the art would deny this. A

few of the differences that come readily to mind are, for example, that with DNA one is concerned with chemical stability, efficiency of uptake, stable retention, and subsequent expression of the injected molecule into target cells, whereas with cells separate issues of formation of effective attachment to ECM and neighboring cells, short- and long-term viability, and responses to environmental cues arise. The expression of the recombinant cDNA would be under control of the limited number of enhancer and promoter elements in the plasmid, as opposed the native control elements with the genome. Therefore, even equivalent gene doses would not be expected to yield equivalent amounts of gene product with a plasmid as opposed to a cell. Furthermore, the rejection pointed out that, unlike $phVEGF_{165}$, a cell is not a single molecule designed for expression of a single gene. Applicant apparently missed that point. Every cell expresses thousands of genes and cells possess characteristics and abilities that cannot be accounted for by the presence or absence of a single gene product. One of skill in the art, upon reading "VEGF cDNA" *might* think "stem cells" if secretion of VEGF were thought to be a characteristic of stem cells. Such a supposition would be contrary to the state of art at the time the invention was made, and a person of skill in the art would have no reason to make such a supposition.

38. All of these reasons were presented to Applicant as to why one of skill in the art at the time of filing would not expect plasmid DNA and genomic DNA to be comparable on a per weight basis. The Declarants did not address these issues, and Applicant merely refers back to pages 10 and 11 of Applicant's remarks to suggest the unfounded counter assertion that "the Examiner has proffered no objective evidence that cells and cDNA clones function differently". Furthermore, one of skill in the art would understand that the factors that

influence the efficacy of administration of DNA vs. cells can work in opposite ways (*i.e.* tending to require a higher input or permitting a lower input) and the net result cannot be predicted with mathematical precision. Applicant's formula certainly does not rise to the level of a mathematical model that takes all of these factors into account. Therefore, Applicant's assertion (p.20) that the result of the extrapolation overlaps with the number of cells used by Strauer et al. (2002) is irrelevant because it is pure coincidence. Furthermore, even if Applicant had stumbled upon a simple method for determining cell numbers to use in therapy, this would not support any argument for enablement of the instant claims. Such a method would be new to the art and the skilled artisan would not be aware of it unless the specification specifically taught it. Examples 17 and 18 DO NOT describe direct injection of cells. The 6.25×10^6 and 12.5×10^6 cell numbers do not appear in the specification. A method for deriving these cell numbers is not in the specification. Examples 17 and 18 do not describe any method using cells. Examples 17 and 18 do not direct the skilled artisan to use any kind of cell in place of the VEGF cDNA in the examples. They do not suggest the use of stem cells or any kind of cell, or suggest any method wherein cells are administered to grow an artery or any other organ. Guidance for the use of cells is not present in Examples 17 or 18, not even implicitly.

39. Applicant repeatedly cites Example 18 as teaching the use of cells. If Applicant intends to persist with this line of argumentation, Applicant is advised, in the interest of advancing prosecution, that this line of argumentation is totally without merit and will never be found persuasive in any sense. Stem cells are not equivalent to cDNA clones. Applicant has asserted (p.12) that Dr. Elia was the first to recognize that VEGF, cDNA, and stem cells are

equivalent species within the genus soft tissue growth promoters for growing arteries in a human patient. In so arguing, Applicant implicitly acknowledges that at the time the instant application was filed, methods of *in vivo* treatments involving administering whole live cells as opposed to administering nucleic acids had a different status in the art such that cell therapy and gene therapy were understood to not be obvious variants of one another. For one of skill in the art to *even think* of extrapolating example 18 to guide the use of cells, the skilled artisan would have to already know the very thing that Applicant claims to have been the first to discover. The instant specification does not provide any evidence to cause the skilled artisan to make this conceptual leap.

40. Pages 20-23 of Applicant's remarks are mainly addressed to the following key conclusions of the rejection of record: (1) the instant specification adds no new technical advance beyond that which is taught in Isner et al (*Circulation.* 1995;91:2687-2692), (2) to say that these non-obvious and remarkable results (referring to growth of an artery by implanting cells) can be achieved without doing a single experiment is incredible, and (3) Applicant claims to have achieved something no one else had done, and then claims to have achieved it simply by writing it down. Applicant alleges (p.20) that the PTO issued the Isner '887 and Kornowski et al. '832 patent, which have a scope of claims including treating human patients using cell therapy, based on "prophetic" disclosures but contained no human examples. According to Applicant, these issued patents indicate that Dr. Elia's improvement to the medical arts has fostered prejudicial skepticism because of its manner of reduction to practice. The Examiner will not comment, and is indeed forbidden from commenting, on the validity of an issued patent. In view of Applicant's perception of having received "extra statutory/regulatory

negative responses", the following facts are noted. First, the USPTO cannot, and does not, demand human clinical trials to demonstrate enablement for claims to methods of treating humans. Nothing in the rejections of record can logically be taken to imply such a demand. Nearly all patents in which biotechnological inventions are directed to the treatment of humans rely on animal, or even in vitro, evidence that the claimed methods are supported by a sound scientific basis, that the methods can work, and to provide enough guidance so that application to humans can proceed with a reasonable expectation of success. The '887 patent disclosed experimental evidence of vascular growth after administration of progenitor cells in art-accepted experimental models (see Figs. 6-8, for example). Likewise, the '832 patent provides both in vitro and in vivo examples in support of the claimed subject matter. For instance, Example 4 provides functional and histological evidence of new blood vessel formation after autologous bone marrow transplantation in an animal model of chronic myocardial ischemia. Thus, the examples that support the allowed claims are "prophetic" only in that the methods were not demonstrated in humans. The sufficiency of the evidence is judged on a case-by-case basis. The instant specification provides no comparable evidence upon which to base a judgment. Therefore, Applicant's insinuation that the instant application has received "extra statutory/regulatory negative responses from the PTO vis-à-vis the '887 and '832 patents" is totally without merit and finds no support in the record.

41. On page 21 and separately on page 22, Applicant makes reference to application serial no. 08/087,185, which was granted as U.S. Patent No. 5,397,235, which predates the Isner et al. Circulation publication by almost two years and is alleged to teach that active compositions/matrices such as, allografts (transplanted cells, such as bone marrow stem

cells), promote the growth of gum (soft) tissue. The single appearance of the term "allograft" in the '235 patent occurs in the paragraph spanning columns 6-7. The paragraph is about hydroxyapatite and other materials that may be used for packing material in dental implants and contains the following sentences:

> "These matrices can be porous, non-porous, active and/or resorbable matrices, or totally inert. For example, coral and coral analogs, polymethyl methacrylate, polyethylene, PTFE (polytetrafluroethylene), polysufone, polymers, polyethylene glycols, osteomin (bone ash), autogenous bone, freeze dried demineralized bone, resorbable and non-resorbable hydroxyapatite, xenographs (bovine), miniscrews, allografts, composites, polyethylene glycol propionaldehyde, HAPSET, or the patient's own bone can be utilized."

42. Applicant argues that this single mention of allographs teaches that bone marrow stem cells promote the growth of tooth gum, which comprises blood vessels, which includes arteries. Applicant further argues that this teaching represents a contribution to the medical art that both predates and goes beyond the Isner et al., 1996 publication of record, which teaches the use of VEGF cDNA to promote blood vessel formation. What a stretch! Neither bone marrow stem cells nor arteries are mentioned, even once, anywhere in patent 5,397,235. Furthermore, the most straightforward interpretation of "allografts" in the given context, is that it refers to *bone* allografts. How does one derive "bone marrow stem cells" from a list that includes coral, polymethyl methacrylate, freeze dried demineralized bone, and miniscrews? Applicant (p.21) apparently refers to the sentence, "These matrices can be porous, non-porous, active and/or resorbable matrices, or totally inert", to argue that because the list includes both inert and active substances, "allograft" should be understood to mean an active substance, which would suggest bone marrow stem cells. At best, such an argument would rely on the notion that the teaching of a genus (allografts) automatically includes

teaching of every species within the genus. This is both contrary to law and contrary to common sense. The assertion that patent 5,397,235 establishes that Dr. Elia was the first to recognize the role of bone marrow cells in achieving the remarkable result of growing a new artery is totally without foundation. Even if the single reference to "allografts" in patent 5,397,235 were, through Applicant's tenuous logic, construed to convey the concept that bone marrow stem cells *can be used* to grow an artery, it could not possibly be construed as a teaching of *how to* use stem cells to grow an artery.

43. On page 23, Applicant takes issue with the discussion of the relation of obviousness to enablement in the previous office action. Applicant urges that the obviousness issue does not have merit because "Applicant has never argued "that growth of an artery using stem cells was obvious in view of prior art in 1998."" Applicant further asks for an explanation for how the Court's decision in KSR v. Teleflex, 82 USPQ 2d 1385 (US 2007) dealing with "obviousness" (35 U.S.C. §103) pertains to the enablement rejection at hand. It is agreed that Applicant did not *intentionally* say that growth of an artery using stem cells was obvious in view of prior art in 1998. Applicant had previously attempted to attach significance with respect to enablement to the absence of rejections of the instant claims over prior art. The teachings of Isner et al., (*Circulation.* 1995, 91:2687-2692; of record) differ from the methods of the instant claims only teaching administration of a cDNA encoding protein growth factor whereas the instant claims recite administration of stem cells. The rejection of record made the point that Applicant's arguments trivialize the differences between the prior art and the claimed methods. As part of the response filed 04/30/2007, Applicant had insinuated that the difference between the art of record and Applicant's claimed method

could be bridged by "common sense". In *KSR*, the Court found that the product of ordinary skill and common sense is likely not the product of innovation. Thus, by evoking "common sense", Applicant had made a case, albeit unintentionally, that the instant methods are obvious in view of the prior art. The rejection of record holds that starting with knowledge that a purified growth factor or a cDNA that encodes a growth factor can stimulate artery formation (*i.e.* the prior art knowledge in US 4296100 and Isner *et al.* 1995, of record), it is not obvious for one to achieve the same result using a stem cell or any other kind of cell.

44. Finally, on page 24, Applicant argues that any *prima facie* case of lack of enablement has been rebutted by the submission of the multiple Declarations of experts in the medical field. This had been addressed in the record. Case law has established that anticipation and operativeness are questions of fact; however, obviousness and enablement are questions of law. See In re Lindell, 155 USPQ 521; In re Chilowsky, 134 USPQ 515. The experts have given an opinion as to the ultimate legal conclusion of enablement, to which no weight is given. The underlying basis for the legal conclusion has been considered in this and every office action in the record.

45. Therefore, for the reasons detailed herein and for reasons of record, claims 403-405 and 407 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Double Patenting

46. Provisional rejection of claims 403-405 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 163 and 170-173 of copending

Application No. 10179589 is maintained for reasons of record. Applicant's intent to file a terminal disclaimer upon an indication of allowable subject matter is acknowledged.

New Double Patenting Rejection Necessitated by Amendment

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

47. Claims 403 and 407-412 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 161-164 and 172-174 of copending Application No. 10179589. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Independent claim 174 in the '589 application, introduced by amendment subsequently to the previous office action in the instant case, recites a method of producing and integrating an artery at a selected site in a body of a human patient comprising placing a cell in a body of a human patient and growing said desired artery, which is identical in scope to independent claim 403 in the instant application. In accordance with Applicant's arguments on pages 7 and 21 of the Response filed 11/28/2007, Step (b) of instant claim 403 is interpreted as reciting an intrinsic step of artery formation that does not require action on the part of the practitioner of the method. Dependent copending claims 161-164, 172 and 173 and instant claims 407-412 add identical limitations to their identical base claims.

Conclusion

48. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
5 May 2008

/David S Romeo/
Primary Examiner, Art Unit 1647